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**Versatile synthesis and rational design of caged morpholinos.**

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**Public Summary:**

**Scientific Abstract:**

Embryogenesis is regulated by genetic programs that are dynamically executed in a stereotypic manner, and deciphering these molecular mechanisms requires the ability to control embryonic gene function with similar spatial and temporal precision. Chemical technologies can enable such genetic manipulations, as exemplified by the use of caged morpholino (cMO) oligonucleotides to inactivate genes in zebrafish and other optically transparent organisms with spatiotemporal control. Here we report optimized methods for the design and synthesis of hairpin cMOs incorporating a dimethoxynitrobenzyl (DMNB)-based bifunctional linker that permits cMO assembly in only three steps from commercially available reagents. Using this simplified procedure, we have systematically prepared cMOs with differing structural configurations and investigated how the in vitro thermodynamic properties of these reagents correlate with their in vivo activities. Through these studies, we have established general principles for cMO design and successfully applied them to several developmental genes. Our optimized synthetic and design methodologies have also enabled us to prepare a next-generation cMO that contains a bromohydroxyquinoline (BHQ)-based linker for two-photon uncaging. Collectively, these advances establish the generality of cMO technologies and will facilitate the application of these chemical probes in vivo for functional genomic studies.

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